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Confocal Endomicroscopy Characteristics of Different Intraductal Papillary Mucinous Neoplasm Subtypes

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Abstract

Intraductal papillary mucinous neoplasms are classified into gastric, intestinal, pancreatobiliary, and oncocytic subtypes where morphology portends disease prognosis. The study aim was to demonstrate EUS-guided needle-based confocal laser endomicroscopy imaging features of intraductal papillary mucinous neoplasm subtypes. Four subjects, each with a specific intraductal papillary mucinous neoplasm subtype were enrolled. An EUS-guided needle-based confocal laser endomicroscopy miniprobe was utilized for image acquisition. The mean cyst size from the 4 subjects (2 females; mean age = 65.3±12 years) was 36.8±12 mm. All lesions demonstrated mural nodules and focal dilation of the main pancreatic duct. EUS-nCLE demonstrated characteristic finger-like papillae with inner vascular core for all subtypes. The image patterns of the papillae for the gastric, intestinal, and pancreatobiliary subtypes were similar. However, the papillae in the oncocytic subtype were thick and demonstrated a fine scale-like or honeycomb pattern with intraepithelial lumina correlating with histopathology. There was significant overlap in the needle-based confocal laser endomicroscopy findings for the different intraductal papillary mucinous neoplasm subtypes; however, the oncocytic subtype demonstrated distinct patterns. These findings need to be replicated in larger multicenter studies.

Keywords

Microscopy; Confocal; Pancreatic Neoplasms

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Conflicts of Interest

The authors have no conflicts of interest to report.

INTRODUCTION

Pancreatic cancer is a leading cause of cancer-related mortality in the United States. There has been a greater emphasis on early detection of pancreatic lesions in individuals at high-risk for pancreatic cancer. Intraductal papillary mucinous neoplasms (IPMNs) are cystic precursor lesions of pancreatic cancer. IPMNs are classified by location of involvement into main duct and branch duct types, and by histology into gastric, intestinal, pancreatobiliary, and oncocytic subtypes [1]. Main duct involvement portends a worse prognosis compared to the branch duct type [2]. IPMN morphology has been shown to be an independent predictor of patient prognosis where oncocytic and pancreatobiliary subtypes are associated with adverse malignant potential and clinical outcomes [3].

While current guidelines recommend surgical resection of IPMNs with high-risk features, they do not include pathological subtype in risk stratification. Pre-operative identification of IPMN subtype can potentially influence long-term management and outcomes. Pancreatic juice cytology with mucin (MUC) staining may be useful in the preoperative diagnosis of IPMN subtypes [4]. However, at present, there is a lack of data on pre-operative identification of IPMN subtypes and presence of high-grade dysplasia.

Confocal laser endomicroscopy (CLE) is a laser-guided microscopic imaging system that allows for real time histopathology of tissue structures via fluorescence contrast [5]. While differentiating mucinous from non-mucinous cystic lesions is clinically challenging, CLE has been previously successful in diagnosing IPMNs [5]. The objective of this study was to demonstrate EUSnCLE imaging features of the four subtypes of IPMNs and to correlate their features to histopathology using representative cases in a pre-surgical setting.

Patients and Methods

Patients (n=3) with the gastric, intestinal, and pancreatobiliary IPMN subtypes were among participants enrolled in a prospective study (INDEX trial; ClinicalTrials.gov NCT02516488) at The Ohio State University Medical Center. One patient with the oncocytic subtype was managed at the Indiana University Hospital. This case series is a retrospective analysis of the four patients highlighted previously, each with one of the four IPMN subtypes, including gastric, intestinal, pancreatobiliary, and oncocytic subtypes. Prior approval from the respective Institution Review Boards was obtained.

Data Collection

Patient history, demographics, comorbidities, laboratory, and imaging findings were collected using a standardized data collection form. EUS was performed to determine the size of the cyst, location, compartments, presence or absence of main pancreatic duct dilation, septation, internal debris, mural nodules, and wall thickness. Fine needle aspiration (FNA) was performed after nCLE to obtain cyst fluid for CEA and amylase levels, and cytology.

EUS-nCLE Technique

All EUS examinations were completed using the standard linear echoendoscope (Olympus America, Center Valley, PA, USA). Fluorescein (5 mL of 10% fluorescein sodium) was injected intravenously (IV) 2–3 minutes prior to CLE imaging. The AQ-Flex nCLE miniprobe (Cellvizio, Mauna Kea Technologies, Paris, France) was preloaded into a 19-gauge Flex (Nitinol) needle (Boston Scientific, Natick, MA, USA) and secured in place by a locking device. The preloaded needle was inserted into the echoendoscope and under EUS guidance, advanced into the lesion of interest via transduodenal or transgastric route. The nCLE probe was then advanced beyond the tip of the FNA needle until it made a soft contact with pancreatic cyst epithelium of a wall or inner mural nodule. Intracystic endomicroscopic images were obtained with permitted angulation of the 19-gauge needle. After image acquisition was complete (generally after 6–8 minutes), the locking device was subsequently released and the AQ-Flex miniprobe was removed from the FNA needle. A syringe with negative suction was attached to the proximal end of the FNA needle and cyst fluid was collected. A dose of IV fluoroquinolone was administered on the day of the procedure and oral quinolone was continued for three days afterwards.

Histopathology

All IPMN lesions underwent surgical resection and standard pathology processing for identification of specific subtypes.

Data Analysis

A specially designed software program (Cellvizio Viewer; Mauna Kea Technologies, Paris, France; free for download) was used to review all nCLE images and videos. After review of surgical histopathology, a post-hoc frame-by-frame review of all nCLE videos was performed.

RESULTS

Study Cohort

A total of 4 subjects (2 male, 2 female) with a mean age of 65.3±12 years underwent EUS-nCLE with subsequent surgical resection and histopathology analysis. Clinical, imaging, EUS, and pathological features are listed in Table 1. The mean size of these lesions was 37±12 mm. All lesions demonstrated mural nodules and focal dilation of the main pancreatic duct indicating a mixed duct IPMN. Three patients presented with related abdominal pain as the presenting symptom that prompted cross sectional imaging with discovery of the pancreatic cystic lesions (PCLs).

Histopathology

The histopathology associated with each IPMN subtype is illustrated in Figure 1. Pancreatobiliary IPMN consisted of cells resembling cholangiobiliary neoplasms and demonstrated short, complex papillae with occasional cribriform structures. Gastric IPMN demonstrated thick finger-like papillae and resembled gastric foveolar epithelium with pyloric-type glands in the periphery. Intestinal IPMN resembled intestinal villous adenomas

with tall columnar epithelial cells, pseudostratification, and presence of goblet cells. Oncocytic IPMN revealed thick complex papillae with intraepithelial lumina and neoplastic cells with abundant, intensely eosinophilic cytoplasm.

EUS-guided nCLE

All IPMN lesions had characteristic epithelial bands with finger-like projections or papillae (Figure 1). The papillae appeared as dark bands, which represent the outer epithelium, surrounding a central lighter area, which represents the inner vascular core. The papillae were easily and consistently observed in all 4 cases. These papillae are observed in various configurations based on the location of the nCLE probe. While characteristic finger-like appearance is most suggestive, other variations include ‘alternating light and dark bands’ and a ‘target’ or ‘dough-nut’ configuration with outer epithelium and inner vascular core. Due to the extensive vascularity, the background appeared generally bright in all IPMNs with high uptake of IV fluorescein.

An important distinction that was observed for the oncocytic IPMN subtype is that the papillae demonstrated multiple fine clefts and scale-like appearance within the papillae (Figure 2). This appearance is secondary to their characteristic intraepithelial lumina, which was also observed in histopathology (Figure 2). The image patterns of the papillae for the gastric, intestinal, and pancreatobiliary subtypes were generally similar without delineating distinctive features.

DISCUSSION

In this case series, we demonstrate that EUS-nCLE has the ability to provide diagnostic imaging of IPMNs and potentially identify the oncocytic subtype in a preoperative setting. While the pathological features of other subtypes were not easily distinguishable on EUS-nCLE, the oncocytic subtype demonstrated fine fissures and a scale-like appearance of the papillae corresponding to the pathologically documented intraepithelial lumina [6]. These distinctive features may be relatively specific for oncocytic IPMN that often give the proliferation an arborizing cribriform architecture when observed either longitudinally or in cross-section. Since the nCLE (AQ-Flex miniprobe) has a maximum lateral resolution of 3.5 μm, these relatively larger epithelial characteristics can be observed. To our knowledge, this is the first study describing pre-surgical EUS-nCLE findings in definitively diagnosed IPMN subtypes.

The defining feature of IPMN lesions on nCLE imaging is the finger-like papillae, which consists of an outer epithelium and an inner vascular core, consistent with prior studies [5]. Although all IPMN subtypes have similar morphologic features, considerable variability exists between pathologists in diagnosing them. In one study, five gastrointestinal pathologists were able to achieve a consensus diagnosis for only 58% of cases [7]. This could imply similar variabilities in EUS-nCLE guided differentiation of IPMN subtypes. For conclusive differentiation, pathologists utilize immunohistochemistry of mucin core proteins (MUCs) since each IPMN subtype has a unique immunoprofile [7, 8]. Since nCLE can only identify the distinguishing characteristics of the oncocytic subtype, perhaps future focus should be more on detecting high-grade dysplasia than categorizing the four subtypes.

In addition to morphologic differences, the oncocytic subtype is also genetically distinct from the other IPMN subtypes, as it does not typically harbor the traditional IPMN mutations such as KRAS [9]. The characteristic histopathologic pattern seen with the oncocytic subtype consists of arborizing papillae with cells exhibiting prominent nucleoli and intraepithelial lumina [9]. It is important to note that oncocytic IPMN typically occurs in the main pancreatic duct and can have recurrences several years after resection [10]. Additionally, both oncocytic and pancreatobiliary IPMN subtypes are associated with more frequent high-grade dysplasia, which predisposes them to develop into invasive carcinomas [8].

Additional studies are necessary to confirm these findings before they become defining features of IPMN lesions given the small study sample size of four cases. Additionally, nCLE image acquisition is limited by the angulation of the 19-gauge needle and there may have been areas of the PCL that may not have been imaged. Lastly, intraobserver variability may exist in interpreting and analyzing the nCLE image patterns.

The addition of nCLE-based epithelial features to the standard evaluation of PCLs may improve the pre-operative diagnostic evaluation of PCLs. Overall, there was significant overlap in the EUS-nCLE imaging for the different IPMN subtypes; however, the oncocytic subtype demonstrated distinct nCLE patterns. The small sample size of the case series limits the generalizability of these patterns. Nevertheless, these findings suggest that additional investigations are necessary including exploring the potential of EUS-nCLE for detecting high-grade dysplasia and risk stratification of IPMN lesions.

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Abbrevations

nCLE	needle-based confocal laser endomicroscopy
IPMN	intraductal papillary mucinous neoplasm
PDAC	pancreatic ductal adenocarcinoma

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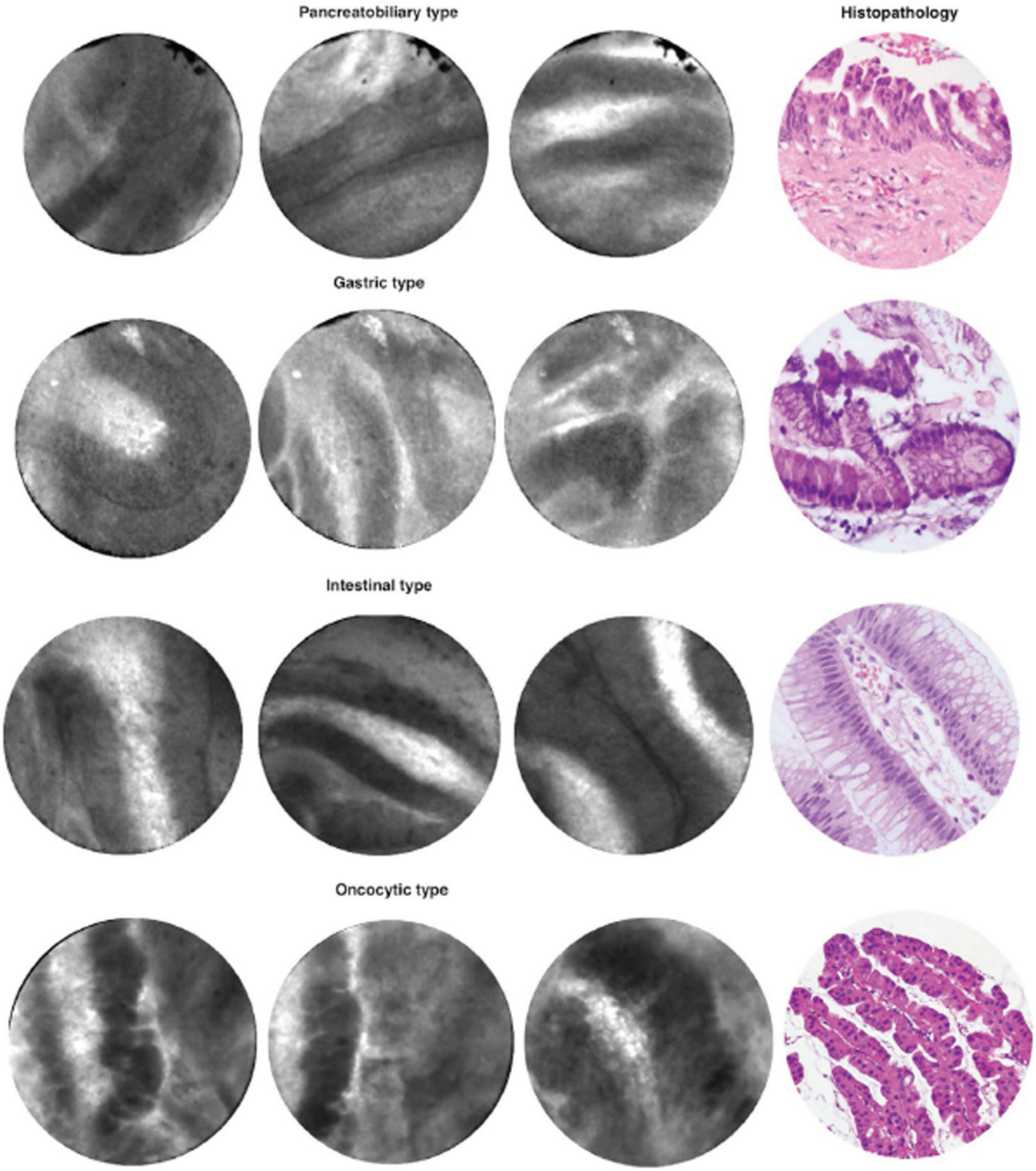

Figure 1.

A comparison of the needle-based confocal laser endomicroscopy and histopathology findings for pancreatobiliary, gastric, intestinal, and oncocytic subtypes of intraductal papillary mucinous neoplasms: the oncocytic IPMN subtype demonstrates papillae with multiple fine clefts and scale-like appearance due to characteristic intraepithelial lumina.

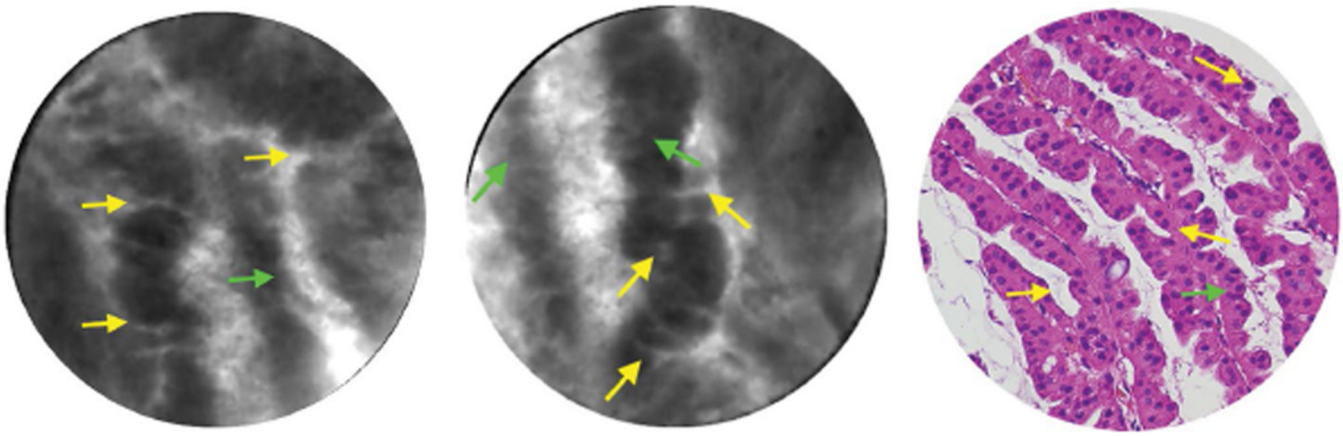

Figure 2.

Oncocytic subtype intraductal papillary mucinous neoplasm demonstrating intraepithelial lumina (yellow arrows). The entire papilla of interest is bounded by the green arrows. There is good correlation between needle-based confocal laser endomicroscopy and histopathology findings.

Table 1

Demographics, clinical features, EUS and FNA characteristics and findings, and final diagnosis of patients with intraductal papillary mucinous neoplasms (IPMNs).

	1	2	3	4
Gender	Female	Male	Female	Male
Age (years)	67	71	75	48
History of pancreatitis	No	No	Yes	No
Diabetes Mellitus, type 2	Yes	Yes	No	No
Abdominal symptoms	Symptomatic	Incidental	Symptomatic	Symptomatic
EUS features				
Size (mm)	21×18	40×25	36×14	50×38
Location	Head	Head	Body	Body/neck
MPD communication or dilation	Yes	Yes	Yes	Yes
Compartments	Multiple	Multiple	One	Multiple
Septation	Thin	Thin	Thin	Thin
Internal debris	No	No	No	Yes
Wall thickness	No	Variable	No	Yes
Mural nodule	9 mm hypoechoic nodule	14 mm solid (mural) nodule	Calcified mural nodule	Hyperechoic, irregular mural nodule (22×18 mm)
FNA				
Route	Transduodenal	Transduodenal	Transgastric	Transgastric
Quantity (FNA; mL)	3	1	4	5
Fluid characteristics	Clear, viscous, visible mucous material	Viscous	Clear, serous, slightly viscous	Thin
Cyst CEA (ng/dL)	188	Fluid too thick to measure	148.3	53
Cyst amylase (IU/dL)	>10,000	Fluid too thick to measure	7,583	Not performed
Cytology	Mucin and clusters of epithelial cells with moderate atypia	Scant mucin	Scant mucin	Numerous epithelial cells with abundant, granular and vacuolated cytoplasm
Final diagnosis	Gastric type IPMN	Intestinal type IPMN	Pancreatobiliary type IPMN	Oncoytic type IPMN

CEA carcinoembryonic antigen; MPD main pancreatic duct